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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,601	04/03/2000	BERNARD ABRAMOVICI	IVD994	2604
27546 7590 02/20/2004 SANOFI-SYNTHELABO INC. 9 GREAT VALLEY PARKWAY P.O. BOX 3026 MALVERN, PA 19355			EXAMINER JAGOE, DONNA A	
			ART UNIT 1614	PAPER NUMBER

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/446,601	ABRAMOVICI ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 and 9-22 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 9-22 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

Claims 1-7 and 9-22 are pending in this application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 October 2003 has been entered.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

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not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 and 9-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Physicians Desk Reference in view of Story et al. U. S. Pat. No. 4,944,949 and Martin-Algarra et al. Internat. J. of Pharmaceutics, the secondary references being considered together.

The claims are drawn to a pharmaceutical composition of a benzofuran derivative such as amiodarone or dronedarone solubilized with a nonionic hydrophilic surfactant such as polysorbate 80, to be administered orally in a tablet or gelatin capsule with between 1-50% active principle and 5-15% of nonionic hydrophilic surfactant.

The Physicians Desk Reference teaches an oral formulation of amiodarone tablets, formulated with excipients such as colloidal silicon dioxide, lactose, magnesium stearate, povidone and starch. Further, it teaches that amiodarone is slightly soluble in water (see description). It does not teach the surfactants of the instant application.

Story et al. teach a pharmaceutical delivery system of non-ionic hydrophilic surfactants such as polyoxyethylated surfactants, sorbitan fatty acid esters, poloxamers, polyethylene glycol fatty acid esters and polyethoxylated glyceryl fatty acid esters (column 5, lines 23-32) for poorly water soluble active agents such as NSAIDS (column 4, lines 25-32). It differs in that it does not teach the active agents amiodarone or dronedarone. Martin-Algarra et al. teach compositions of amiodarone in a non-ionic hydrophilic surfactant such as polysorbate 80 (see abstract). The aim of the study was

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to characterize intestinal absorption of amiodarone in the presence of increasing non-ionic surfactant concentrations (page 2, column 1, first full paragraph) The concentrations of the surfactant are 0.4 to 80 mM with amiodarone in concentrations of 10-80 micrograms/milliliter (page 2, column 2, lines 7-13). It does not teach oral administration and it does not teach dronedarone.

It would have been obvious to have administered amiodarone orally in a non-ionic hydrophilic surfactant composition since the PDR teaches that amiodarone is slightly soluble in water and the surfactant systems of Story et al. demonstrate the solubilization of insoluble drugs such as NSAIDS. One would have been motivated to use the surfactants of Story et al. since both the NSAIDS of Story et al. and the antiarrhythmics of the instant application are known to be poorly water-soluble. Motivation to formulate amiodarone and dronedarone in a hydrophilic anionic surfactant comes from the need for a rapidly absorbed orally available antiarrhythmic such as amiodarone. It would be expected that dronedarone would behave similarly when solubilized and administered orally since dronedarone is also a benzofuran derivative, it would be expected that it would behave similarly with regard to the solubility data.

Additionally, absorption would be expected to be improved as taught by Martin-Algarra et al., thereby providing additional motivation to do so.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 7, 11, 12, 16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martin-Algarra et al. (U).

The claims are drawn to a pharmaceutical composition comprising a benzofuran derivative such as amiodarone and dronedarone in a non-ionic hydrophilic carrier such as poloxamer 407 in amounts of from 200 to 400 mg in a capsule or tablet.

Martin-Algarra et al. teach amiodarone, a benzofuran derivative, in a non-ionic hydrophilic carrier such as polysorbate 80.

1. It does not teach the benzofuran derivative dronedarone;
 2. it does not teach the non-ionic hydrophilic carrier, poloxamer 407 and;
 3. it does not teach specific amounts such as 200 to 400 mg in a capsule or tablet.
1. It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give

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comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532. It would have been obvious to substitute dronedarone for the amiodarone in Martin-Algarra since both amiodarone and dronedarone are both benzofuran derivatives it is expected that they would behave in a similar manner when placed on the non-ionic hydrophilic carrier, i.e. absorption would be enhanced when given by the oral route.

2. It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532. It would have been obvious to substitute the non-ionic hydrophilic surfactant poloxamer 407 for the non-ionic hydrophilic surfactant polysorbate 80 described in Martin-Algarra. Since they are both non-ionic hydrophilic surfactant they would be expected to behave in a similar manner.

3. As anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and serve as useful guideposts for the physician. The specific safe and effective amount will be vary, with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of the concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the formula therein and the dosage regimen desired for the composition.

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For these reasons it would have been obvious to use 50 to 500 mg of the active principal in the pharmaceutical composition.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 and 9-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 6,143,778 A. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to a pharmaceutical composition of amiodarone, solubilized in a non-ionic hydrophilic surfactant system. Although, the amiodarone of the patent is for parenteral administration, it would have been obvious to lyophilize the compositions of the patent and administer them orally in a tablet or a capsule.

Remarks

It is the applicant's position that the cited references would not have suggested the applicants' invention because if the invention would have been obvious, the absorption problem related to amiodarone would have been solved long ago. In response, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Since the disclosure provided by the PDR recognizes the problem of solubility in amiodarone, the Story reference provides motivation for one to solubilize insoluble drugs using non-ionic hydrophilic surfactants, and Martin-Algarra et al solve the absorption problem of amiodarone specifically by using the non-ionic hydrophilic surfactant, polysorbate 80, a *prima facie* case of obviousness is established.

While the examiner is in agreement with the arguments regarding the Story et al. reference where the applicant recites that "there is nothing in Story et al. that would have suggested using such a small amount of non-ionic hydrophilic surfactant to both increase rate and reduce variability of absorption of either NSAIDS or amiodarone and dronedarone". Clearly, Martin-Algarra et al. recognize the problem that amiodarone has regarding erratic and variable absorption and also recites that a small amount of non-ionic hydrophilic surfactant solves the problem. Martin-Algarra et al. teach the

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absorption rate constants of amiodarone *decreased* as the surfactant concentration *increased* and absorption was unusually fast at *lower surfactant concentrations* (see abstract). Applicant alleges that the Martin-Algarra reference does not disclose oral administration or oral formulations. In response, Martin-Algarra et al. conclude that the convenience of designing a more reliable dosage form of amiodarone, containing a suitable dose of surfactant as a **solid** dispersion are entirely confirmed with polysorbate preparations being preferable (page 6, column 2).

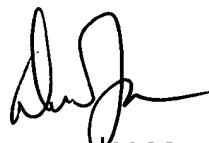
Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 9:00 A.M. - 5:00 P.M..


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (571) 272-0584. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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